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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,632	11/25/1997	ELAZAR RABBANI	ENZ-53(C)	4638

28171 7590 10/14/2011

ENZO BIOCHEM, INC.
527 MADISON AVENUE (9TH FLOOR)
NEW YORK, NY 10022

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
10/14/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,632	RABBANI ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *246-252,255,264,273,274 and 276-279* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *246-252,255,264,273,274 and 276-279* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 07/20/2011 to the Office action mailed 01/20/2011 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 01/20/2011 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Applicant's amendments to the claims filed 07/20/2011 have been entered into the application. With entry of the amendment, claims 246-252, 255, 264, 265, 273, 274 and 276-279 are pending and examined herein.

Response to Arguments

Claim Rejections - 35 USC § 112

The rejection of claim 273 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

The rejection of claim 273 under 35 U.S.C. 112, second paragraph, is maintained. Applicants point to Figure 6 for distinctly pointing out the claimed invention. The claim has been modified to refer to the non-nucleic acid entity that is comprises in the modified nucleotide or nucleotide analog. So it appears from the claim that the third nucleic strand comprises a modified nucleotide or analog along with said non-nucleic acid entity.

The polynucleotide tail of the second strand is not recited to be any specific number of nucleotides, therefore in efforts to examine the invention, the claim is interpreted such that the polynucleotide tail can be two nucleotides that are complementary to a third strand comprising a non-nucleic acid entity.

Claim Rejections - 35 USC § 102

The rejection of claim 271 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Myers (EP 0 273 085; of record) is moot as this claim has been canceled.

Claim Rejections - 35 USC § 103

The rejection of claims 246-252, 255, 264, 265, 274 and 276-279 under 35 U.S.C. 103(a) as being anticipated by Craig et al. (US Patent 5,766,902), Wagner et al. (PNAS 1992 of record) and Perales et al. (Eur. J. Biochem Vol. 226: 255-266) is maintained for the reasons of record.

Applicant's argument is acknowledged but not found persuasive. Applicant appears to argue the references separately and in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues Craig et al. teach the use of an electric field to improve the efficient of receptor mediated uptake. While Craig does teach methods to improve the receptor mediated uptake, Craig et al. also teach methods for enhancing the targeted delivery of nucleic acid molecules to cells by coupling the nucleic acid to a ligand having affinity for a cell surface molecule or receptor as stated earlier. Craig et al. also suggest the use of a fusogenic peptide to facilitate uptake.

Applicant next argues that Wagner et al. do not teach or suggest a nucleic acid comprising a modified nucleotide. In response, Wagner et al. was not cited for this teaching. As stated in the previous Office action, Wagner et al. teach the use of ligand mediated constructs to deliver DNA to cells and state that delivery from endosomes is a limiting step that can be solved by the additional use of a fusogenic peptide such as the influenza hemagglutinin fusogenic peptide, this providing further motivation to incorporate a fusogenic peptide into a construct.

Applicant argues Perales et al. teach away from the claimed method by indicating that noncovalent use of polylysine is the preferred method to bind nucleic acid to a receptor. In response, a reference can be relied upon for all that it teaches, even non-preferred embodiments. Perales et al. discuss the concept of ligand mediated delivery of DNA and outlines the design elements that are useful. Perales et al. teach the DNA ligand needs to be efficiently transported to the nucleus and this active process that requires the use of nuclear localization elements and lists a few proteins for this purpose (see page 262).

Applicant concludes none of the cited references teach or suggest a nucleic acid construct that comprises more than one targeting moiety. The claims are drawn to a chemically modified nucleic acid construct comprising a fusogenic peptide, a ligand to a cell receptor and a non-nucleic acid entity that confers nuclear localization. It would have been obvious to one of ordinary skill in the art to incorporate a fusogenic peptide and a nuclear localization entity into the construct taught by Craig et al. Applicant does not argue why the claimed invention is non-obvious over the combination of the references as a whole. Applicant does not provide arguments as to why one of skill in the art would not incorporate a fusogenic peptide or a nuclear localization entity into the construct taught by Craig et al.

One would have been motivated given Wagner et al. teach transfer of a DNA ligand complex from the endosome is an essential step which can be solved by the use of a fusogenic peptide and Perales et all. teach the use of nuclear localization elements are necessary for active localization of the complex in the nucleus. One of ordinary skill in the art would have expected to be able to incorporate these elements into the construct as the steps are routine and taught in the prior art.

Thus the rejection of record is maintained.

Double Patenting

Claims 246-252, 255, 264, 265, 271, 273, 274 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 245-248, 251, 253, 261-265, 306, and 307 of copending Application No.

08/978,633. New claims 276-279 would have been previously rejected in the previous Office action to the rejection of record applies to these newly added claims.

In the reply filed 09/10/2010, Applicant states the provisional rejection will be addressed once there is an indication of allowable subject matter. The reply does not present arguments pointing out the specific distinctions believed to render the claims, including any newly presented claims, patentable over any applied references (37 CFR 1.111(b)).

The Examiner notes allowable subject matter has not yet been identified. Accordingly, the provisional rejection is maintained for the reasons of record, reiterated above.

New Claim Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 278 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 278 depends from claim 271 which has been canceled and has not been examined because it is unclear what further limitations, without assumption, are encompassed in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 273 is rejected under 35 U.S.C. 103(a) as being unpatentable over Myers (EP 0 273 085; of record) and

The instant specification teaches that cell targeting entities include proteins that have affinity for cell surfaces.

Claim 273 is drawn to a chemically modified double stranded nucleic acid construct comprising a modified nucleotide that comprises a polymer. A modified nucleotide is reasonably considered to embrace any nucleotide that has been changed or altered from its natural form, as occurs when a non-nucleic acid molecule is attached to a nucleotide. Logically, the attachment of a non-nucleic acid entity to a nucleotide, such as a protein, represents a modification to that nucleotide. Therefore, a nucleotide that is linked to a protein is a modified nucleotide that contains a non-nucleic acid moiety.

Myers taught a modified double stranded nucleic acid construct that expresses a protein and therefore messenger RNA (i.e., sense RNA) in a cell. See Fig. 2, Detailed Description of the Invention, Examples 1-4, and Claims 1-13. The construct comprises double stranded DNA conjugated to at least one molecule of epidermal growth factor (EGF). See column 3, beginning at line 55; column 6, lines 19-20; and Fig. 2. The EGF

molecule, when covalently attached to a double stranded nucleic acid, is shown to facilitate entry of the nucleic acid into the cell (Exs. 3-5).

The method used to couple EGF to the double stranded DNA results in attachment of EGR to a 5'-phosphate, thereby producing a modified nucleotide (col. 3, line 55). Accordingly, in view of the efficiency and randomness of the chemical reaction, and noting there are only two 5'-phosphates in a linear dsDNA molecule, it is reasonable to presume that the method used by Myers to produce the EGF-dsDNA conjugate results in some dsDNA molecules having one EGF molecule in solely one strand of the dsDNA, as shown in Fig. 2 and as suggested by characterization of the conjugates at column 6, lines 19-20. Thus, the presence of EGF in solely one strand of the nucleic acid is an outcome that is inherent to the method used to make the constructs. Notwithstanding this fact, one of skill would reasonably have predicted that the constructs disclosed by Myers would have the same properties and would function in substantially the same manner regardless of whether the constructs contained one or two molecules of EGF molecules.

It was well known in the art regarding end labeling of oligonucleotide strands for attachment of molecules such as proteins and ligands. Reed et al. teach the use of 3' end modification of an oligonucleotide strand to incorporate polynucleotides that can be linked to ligands.

It would have been obvious to incorporate a linker molecule to the end of the strand for attachment of an EGF molecule more stably. One of skill in the art would

have expected to be capable of making said molecule. Thus the invention was obvious to one of ordinary skill in the art.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1635 Heather Calamita at 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner AU1635